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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,490	MISCHEL ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *16-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The claim amendment filed December 1, 2008, is acknowledged and has been entered. Claims 6, 15 and 20 have been amended. Additionally, the specification amendment filed June 10, 2009, is acknowledged and has been entered.

2. Claims 1-24 are pending in the application.

3. Claims 16-19 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is further noted that the species of additional polypeptide whose presence is detected in the method of the elected invention is phosphorylated-S6 polypeptide.

4. Claims 1-15 and 20-24 are under examination.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, Applicant's amendment and/or arguments filed August 23, 2007, December 1, 2008, or June 10, 2009, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed February 23, 2007.

Grounds of Objection Maintained

Claim Objections

6. The following claims are objected to because of minor informalities:

The objection to Claims 7-10 as not necessarily further limiting the methods of claim 6 and claim 1, is maintained.

In the response, filed August 23, 2007, applicant has traversed this grounds of rejection arguing that the claims properly limit the methods of claim 6 and claim 1 because e.g., claim 7 recites that the use of a phopho-S6 that binds an epitope comprising phosphorylated serine at position 235 in SEQ ID NO:1.

In response, this argument is not found to be persuasive because as set forth in the previous action, the method of claims 6 and 1 do not necessarily examine the presence of phosphorylated S6 ribosomal polypeptide. As set forth in claim 1 only one of (b)-(e) need to be examined, so when the presence of only one polypeptide of (b)-(e) is examined, dependent claims which only recite antibodies that bind to a different polypeptide fail to properly limit the methods of claim 6 and claim 1. Therefore, it is suggested that the claims be amended to properly limit the independent claim, be written in independent form or be canceled.

Appropriate correction is required.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. The rejection of claims 1-15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

(a) The rejection of claims 1-15 as being indefinite in the recitation of "likely to respond" in claims 1 and 13, is maintained.

At page 11 of the response filed August 23, 2007, Applicant has traversed this ground of rejection, arguing that "[w]hen a cell is said to be likely to respond, one of skill will surmise that it means that such cell is more likely than not to respond" and further asked the Examiner to consider the art of Mellinghoff et al. (N. Engl. J. Med. 353(19):2012-2024 (2005) which also "uses the same expression "likely to respond" in

the context of predictive markers".

In response, it is first noted that the claims are directed to methods that identify *tumors*, and not cells, so the relevance of the argument pertaining to cells likely to respond is unclear. Furthermore, it is noted that the claims do not recite the phrase "more likely than not to respond" and Applicant is reminded that limitations are not read into the claims. Finally, with respect to Mellinghoff et al (N. Engl. J. Med. 353(19):2012-2024 (2005), the response did not indicate that a copy of this reference was submitted and a copy of this reference was not found in the submission, so its teachings cannot be properly evaluated, but from Applicant's argument it is not apparent that the art unambiguously characterizes the phrase "likely to respond" as "more likely than not to respond".

Accordingly, while Applicant's response has been fully and carefully considered because the term "likely" is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree of likelihood that the tumor will respond, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Notably, depending upon one's point of view, the likelihood that the tumor need respond would vary widely, so one of skill in the art could not unambiguously interpret the claims. Since it is unclear how "likely" the response by the tumor must be, the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph and this rejection is maintained.

(b) The rejection of claims 1-15 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps, is maintained. See MPEP § 2172.01.

At page 12 of the response filed August 23, 2007, Applicant has traversed this ground of rejection, and appears to be arguing that ascertaining the expression of PTEN and the presence of phosphorylated S6 polypeptide inherently establishes changes in expression of the markers because the presence of the markers is effected by IHC

scoring as set forth in the examples of the specification.

In response, this argument is not found to be persuasive because although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In this case, the steps only require examining a mammalian glioma tumor sample for the ***expression*** of PTEN polypeptide and examining the same sample for the ***presence*** of phosphorylated S6 ribosomal polypeptide while also containing a wherein clause referring to correlations with potential treatments based on decreased expression of PTEN and decreased phosphorylation of S6 ribosomal polypeptide. However, since the active process steps do not actually measure changes in expression of PTEN or phosphorylation of S6 ribosomal polypeptide phosphorylation, it is maintained that the claims omit steps of determining either increased or decreased expression of PTEN and increased or decreased phosphorylation of S6 ribosomal polypeptide. Therefore, it is unclear what steps are actually required to make these correlations and measure these changes in expression and phosphorylation.

Accordingly, while Applicant's response has been fully and carefully considered it is maintained that the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second.

(c) The rejection of Claims 1-15 and 20-24 for reciting SEQ ID Nos in parentheses in claims 1, 7, 9, 13, 15, 20, 22 and 23 (e.g., see claim 1 which recites (SEQ IN NO:7), etc), is maintained.

At page 12 of the response filed August 23, 2007, Applicant has traversed this ground of rejection, and appears to be arguing that the rejection should be withdrawn because the claims are in compliance with the sequence requirements of 37 CFR 1.821.

In response, this argument is not found to be persuasive because this rejection was not made over a sequence compliance issue. As set forth in the last office action,

because the SEQ ID Nos are in parentheses it is unclear if these parenthetical references are meant to further limit the claim, or if the SEQ ID Nos are merely exemplary of polypeptides they follow. Furthermore, if the recitation in parentheses is intended to limit the subject matter claimed, it is unclear if the polypeptide must comprise or consist of the amino acid sequence. Therefore, the claims cannot be unambiguously construed.

Accordingly, while Applicant's response has been fully and carefully considered it is maintained that the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second.

Amending the claims to recite that the polypeptides comprise or consist of the amino acid sequence of a particular SEQ ID NO, for example, would obviate this rejection.

(d) The rejection of Claims 2 and 3 for reciting the limitation "is determined", is maintained.

At page 12 of the response filed August 23, 2007, Applicant has traversed this ground of rejection, and appears to be arguing that the rejection should be withdrawn because the claims are drawn to the detection of a phosphorylated peptide.

In response, this argument is not found to be persuasive because claims 1 examines a sample for the presence of the a phosphorylated peptide, and does not determine phosphorylation, *per se*. Therefore it is unclear if the determination of the phosphorylation of the polypeptide would necessarily be the same as examining for the presence of the phosphorylated polypeptide. Accordingly, due to the ambiguity of using the terminology "is determined" which lacks proper antecedent basis in claim 1 which recites "examining", the claims cannot be unambiguously construed.

Accordingly, while Applicant's response has been fully and carefully considered it is maintained that the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled

artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. The rejection of claims 1-15 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Starting at page 12 of the amendment filed August 23, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

In this case, Applicant appears to argue that examples 3-8 in the specification enable the claimed methods for identifying a mammalian glioma tumor that is likely to respond, or is responsive to an EGFR polypeptide (SEQ ID NO: 7) inhibitor or an mTOR polypeptide (SEQ ID NO: 2) inhibitor because the examples 3-6 provide experiments which correlate expression levels of the various markers and because examples 7-8 examines the prognostic relevance of data.

In response, this argument is not found persuasive because as set forth in the previous action the use of the *claimed invention* has not been exemplified; and moreover, there is no guidance or exemplification present in the specification that provides a predictive correlation linking e.g., *levels of expression of PTEN polypeptide and* phospho-S6 ribosomal polypeptide, before, and in the absence of, treatment with any specific treatment regimen. Once again the claims recite the object of identifying a mammalian glioma tumor that is likely to respond, or is responsive to an EGFR polypeptide (SEQ ID NO: 7) inhibitor or an mTOR polypeptide (SEQ ID NO: 2) inhibitor and none of the examples establish any correlation of *levels of expression of PTEN polypeptide and phospho-S6 ribosomal polypeptide* which is predictive of a mammalian glioma tumor that is likely to respond, or is responsive to an EGFR polypeptide (SEQ ID NO: 7) inhibitor or an mTOR polypeptide (SEQ ID NO: 2) inhibitor.

Notably, while examples 3-6 look at marker levels, they do not correlate marker levels with any determination of whether a mammalian glioma tumor is likely to respond, or is responsive to an EGFR polypeptide (SEQ ID NO: 7) inhibitor or an mTOR polypeptide (SEQ ID NO: 2) inhibitor based on these levels. Then with respect to example 7, this example is looking at the levels of the markers as they correlate to survival and progression of the disease and does not correlate any levels with a patient's likeliness to respond to an EGFR polypeptide (SEQ ID NO: 7) inhibitor or an mTOR polypeptide (SEQ ID NO: 2) inhibitor. Finally, while example 8 discloses that there is a substantial reduction in S6 phosphorylation in tumor samples from 4 out of 5 glioblastoma multiforme patients treated for 5 days with the mTOR inhibitor, rapamycin, prior to obtaining the sample, as compared to the level of phosphorylated S6 in a tumor sample obtained before treatment from the corresponding patient, and that this inhibition of S6 phosphorylation correlates with diminished tumor proliferation in these four patients (see page 41, example 8 and Figures 3A and 3B), this example looks at the marker levels in tumors that are known to respond to an mTOR inhibitor so it provides no information about whether the markers levels identify a mammalian glioma tumor is likely to respond, or is responsive to an EGFR polypeptide (SEQ ID NO: 7) inhibitor or an mTOR polypeptide (SEQ ID NO: 2) inhibitor. Notably, *the specification is*

silent as to the PTEN status in the glioblastoma multiforme tumors of the patients that were shown to be responsive, or not, to rapamycin treatment in Figure 3; yet, the claimed process necessarily involves an analysis of the likely responsiveness of the glioma cells to the drug (e.g., rapamycin), which depends upon a correlation between the level of one or more markers in the cells and the presence, absence, or insufficiency of PTEN. These correlations are not established by the data presented in Figure 3. Rather it is submitted that, at best, the data in Figure 3 merely show the *not* unexpected finding that following treatment with the mTOR inhibitor rapamycin, glioblastoma cells produce lower amounts of activated, phosphorylated S6 protein and have relatively decreased proliferation rates, as the prior teaches would generally be the case, since S6 acts downstream of mTOR in a signaling pathway leading to cellular proliferation. Figure 3, however, does not correlate the proliferation rate of cells treated with rapamycin, or any other inhibitor of either mTOR or EGFR, and level of S6 phosphorylation in the presence and absence or reduction of PTEN. Consequently, the amount of guidance, direction, and exemplification is not sufficient to reasonably enable the skilled artisan to practice methods commensurate with the scope of the claims because if fails to establish the correlations upon which the claimed invention is based.

Secondly, applicant appears to argue that they are "seeking to obtain claims directed to methods based on those predictors Applicants have actually identified, which provide the basis of the claims" (see page 13 of the response).

In response, this argument is not found persuasive because as set forth in the previous office action, "the specification only provides guidance or exemplification that identifies a glioblastoma multiforme as responsive to a mTOR inhibitor when mTOR is shown to decrease the phospho-S6 ribosomal polypeptide present in a tumor sample as compared to a sample from the same patient before treatment". Furthermore, Applicant's response does not identify these correlations in the specification and does not explain how the specification establishes these correlations. As set forth above, examples 3-8 do not establish expression levels of the claimed polypeptides which correlate with mammalian glioma tumors that are likely to be responsive, or are responsive to an EGFR polypeptide inhibitor or an mTOR polypeptide inhibitor.

Therefore, it is maintained that one of skill in the art would be subject to undue experimentation to determine if any of the claimed expression patterns before treatment or change in expression patterns after treatment of these biomarkers could predictably identify a glioma as likely to respond or responsive to a mTOR polypeptide inhibitor or EGFR polypeptide inhibitor.

Finally, at page 14 of the response Applicant argues that the evidence required to satisfy enablement of the claimed methods is not tantamount to the clinical trial evidence required for FDA regulatory approval and that the specification provides legally sufficient evidence to satisfy the enablement requirement because Example 8 provides a correlation with Ki-67 expression and Example 7 provides correlations between marker levels and time to progression and overall survival.

In response, the Examiner does not hold the position that clinical trial evidence is required for enablement of the claimed methods to identify a glioma as likely to respond or responsive to a mTOR polypeptide inhibitor or EGFR polypeptide inhibitor. In this case, the methods only require that the expression of PTEN polypeptide be examined in a glioma tumor sample along with e.g., the presence of phosphorylated S6 polypeptide, but practicing these steps alone would not allow one of skill in the art to achieve the recited objective. As set forth above, example 8 in the specification *is silent as to the PTEN status in the glioblastoma multiforme tumors of the patients* that were shown to be responsive, or not, to rapamycin (an mTOR inhibitor) treatment and this example does not identify marker levels that are predicative of gliomas that would be responsive to a mTOR polypeptide inhibitor. Once again, this example only establishes the *not* unexpected finding that following treatment with the mTOR inhibitor rapamycin, glioblastoma cells produce lower amounts of activated, phosphorylated S6 protein and have relatively decreased proliferation rates, as the prior teaches would generally be the case, since S6 acts downstream of mTOR in a signaling pathway leading to cellular proliferation. Figure 3, however, does not correlate the proliferation rate of cells treated with rapamycin, or any other inhibitor of either mTOR or EGFR, and level of S6 phosphorylation in the presence and absence or reduction of PTEN. Furthermore, since example 7 only looks at the levels of the markers as they correlate to survival and

progression of the disease this example does not identify marker levels that are predicative of gliomas that would be responsive to a mTOR polypeptide inhibitor. Consequently, the amount of guidance, direction, and exemplification is not sufficient to reasonably enable the skilled artisan to practice methods commensurate with the scope of the claims because if fails to establish the correlations upon which the invention is based.

In conclusion, upon careful and full consideration of Applicant's arguments and the factors used to determine whether undue experimentation is required, for these reasons and as explained more fully in the Office action mailed February 23, 2007, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation, and this rejection is being maintained.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. The rejection of claims 1-11 and 13-15 under 35 U.S.C. 102(b), as being anticipated by Neshat et al (PNAS, 98(18):10314-10319, August 2001, IDS filed October 7, 2004), as evidenced by Sharma et al (J. Bioscience, 11:423-433, 1987, of record), is maintained.

Starting at page 14 of the amendment filed August 23, 2007, Applicant has traversed this ground of rejection.

In the response, Applicant argues that while "Neshat et al. provides data

suggesting that (a) PTEN null cell lines have an increased mTOR-dependent S6 kinase activity; and (b) that PTEN null cell lines have enhanced sensitivity to mTOR inhibition [it] does not however go beyond this correlation to arrive to a method according to Claim 1 which contemplates a test relying on a number of alternative parameters (other than PTEN expression and the presence of phosphorylated S6 ribosomal polypeptide)" and therefore does not anticipate the claimed invention.

In response, this argument is not persuasive because the claimed method only requires step (a), i.e., examining PTEN expression, and *at least one* of steps (b)-(e), and step (b) is examining the presence of phosphorylated S6 ribosomal polypeptide. By way of further explanation, while the claimed methods recite alternative parameters, it does not require them. Accordingly, it is immaterial whether Neshat et al teach the alternative parameters because the claimed invention does not require these steps to be performed since the claimed method only requires that *one* of steps (b)-(e) be performed.

For these reasons and the reasons set forth in the previous office action, and after careful and full consideration of Applicant's response, it is maintained that Neshat et al teach methods materially and manipulatively indistinguishable from the claimed method and anticipate the claimed methods.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. The rejection of claims 1 and 12 under 35 U.S.C. 103(a) as being unpatentable over Neshat et al (PNAS, 98(18):10314-10319, August 2001, IDS filed October 7, 2004), in view Strik et al (Cancer, 91(5):1013-1019, March 2001, of record), is maintained.

Starting at page 15 of the amendment filed August 23, 2007, Applicant has traversed this ground of rejection.

In the response, Applicant reiterates the argument presented in the traversal of the 102(b) rejection that Neshat et al only characterizes PTEN expression and the presence of phosphorylated S6 ribosomal polypeptide, but does not teach the other alternative parameters. Applicant further argues that Neshat et al does not teach the intended use of the method to assess cell responsiveness.

In response, the argument that Neshat et al only characterizes PTEN expression and the presence of phosphorylated S6 ribosomal polypeptide, but does not teach the other alternative parameters is not found persuasive for the reasons set forth above in the response to Applicant's traversal of the 102(b) and the Examiner's response is incorporated herein. Furthermore, in response to Applicant's argument that Neshat et al

do not teach the intended use of the claimed method Applicant is reminded that the subject matter of a properly construed claim is defined by the terms that limit its scope. It is this subject matter that must be examined. As a general matter, the grammar and intended meaning of terms used in a claim will dictate whether the language limits the claim scope. Language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation. See also MPEP 2111.02. In this case, the recited preamble merely suggests an intended use of the recited active steps, and for this reason for the purposes of applying prior art, the recited active process steps are broadly, but reasonably being interpreted as not being solely limited to the intended use of the preamble of identifying a mammalian glioma tumor that is likely to be responsive to an mTOR inhibitor or an EGFR inhibitor.

For these reasons and the reasons set forth in the previous office action, and after careful and full consideration of Applicant's response, it is maintained that methods comprising examining a paraffin embedded biopsy sample obtained from a glioma tumor for the expression of PTEN polypeptide and the presence of phosphorylated S6 ribosomal polypeptide are obvious in view of these references as a whole and this rejection is maintained.

16. The rejection of claims 20-24 under 35 U.S.C. 103(a), as being unpatentable over Neshat et al (PNAS, 98(18):10314-10319, August 2001, IDS filed October 7, 2004), in view of Monia et al (US Patent 6,020,199, February 1,2000, of record), is maintained.

Starting at page 15 of the amendment filed August 23, 2007, Applicant has traversed this ground of rejection.

In the response, Applicant reiterates the argument against Neshat et al presented in the traversal of the 102(b) rejection. Applicant further argues that patent '199 does not teach each and every analyte contemplated according to the invention.

In response, the argument against Neshat et al is not found persuasive for the reasons set forth above in the response to Applicant's traversal of the 102(b) and the

Examiner's response is incorporate herein. Furthermore, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, for these reasons and the reasons of record set forth in the previous office action, and after careful and full consideration of Applicant's response, it is maintained that kits comprising an antibody specific for PTEN polypeptide, an antibody specific for S6 ribosomal polypeptide phosphorylated at serine 235, an antibody specific for AKT polypeptide phosphorylated at serine 473, an antibody specific for Ki-67 polypeptide and at least one secondary antibody that binds one of these antibodies are obvious in view of these references as a whole and this rejection is maintained.

Conclusion

17. No claims are allowed.

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRADLEY DUFFY whose telephone number is

(571)272-9935. The examiner can normally be reached on 7-4:30 M-F with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
September 28, 2009